COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Opixaf 2.5 mg and 5 mg film-coated tablets (apixaban)

NL/H/6149/001-002/DC

Date: 9 April 2026

This module reflects the scientific discussion for the approval of Opixaf 2.5 mg and 5 mg film-coated tablets. The procedure was finalised on 29 October 2025. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Opixaf 2.5 mg and 5 mg film-coated tablets, from Fidia Farmaceutici S.p.A.

Opixaf has the following indications at different strengths:

Adults
Opixaf 2.5 mg
The product is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Opixaf 2.5 mg and 5 mg
The products are indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age≥ 75 years; hypertension; diabetes mellitus; symptomatic heartfailure (NYHA Class ≥ II).

The product is indicated for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population
The product is indicated for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, similarity is proven between the new product and the innovator product Eliquis 2.5 mg and 5 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/11/691) since 18 May 2011 by Bristol-Myers Squibb Pfizer EEIG.

The concerned member state (CMS) involved in this procedure was Italy.

II. QUALITY ASPECTS

II.1 Introduction

Opixaf 2.5 mg and 5 mg are film-coated tablets. Each film-coated tablet contains 2.5 mg or 5 mg apixaban as active substance. The two strengths of the film-coated tablets can be distinguished by colour, shape, size and debossing and are as follows:

Opixaf 2.5 mg
Yellow, round, biconvex film-coated tablets, plain on both sides, size approximately 6 mm diameter.

Opixaf 5 mg
Pink, oval, biconvex film coated tablets debossed with “894” on one side and “5” on the other, size approximately 9.8 mm x 5.2 mm.

The excipients are:
Tablet core – lactose, microcrystalline cellulose (PH 102) (E460), croscarmellose sodium (E468), sodium laurilsulfate, and magnesium stearate (E470b).
Film-coating – hypromellose 2910 (E464), lactose monohydrate, titanium dioxide (E171), triacetin (E1518), iron oxide yellow (E172), iron oxide red (E172; only for the 5 mg strength), and purified water.

The two tablet strengths are dose proportional with regard to the tablet cores.

The film-coated tablets are packed in polyvinyl chloride/polyvinylidene chloride-aluminium (PVC/PVdC-Alu) transparent blisters in cartons.

II.2 Drug Substance

The active substance is apixaban, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is practically insoluble in water. For this product, the same polymorphic form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process starts with the manufacturing of an intermediate, in three synthetic steps. The synthesis of the final substance consists of four steps of three chemical transformations and a final purification. No class 1 solvents or heavy metal catalysts are used in the process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification has been established in-house by the applicant and is based on the specification of the active substance manufacturer. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference products, dissolution method development, formulation optimisation studies and manufacturing process development studies. Feasibility to administer the product through a nasogastric tube when following the instructions in the SmPC has been demonstrated. Instructions described in the SmPC on crushed tablets mixed with water, 5% dextrose in water, apple juice, and apple puree are supported by stability data.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process
The manufacturing process consists of dry blending, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients
The excipients, except for the coating materials, comply with Ph.Eur. requirements. These specifications are acceptable. Acceptable in-house specifications are provided for the coating materials.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of Apixaban, identification of colourants, average weight, uniformity of dosage units, loss on drying, assay, related substances, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. Testing results demonstrate nitrosamine levels consistently below 10% of the control limit. Omission of nitrosamine control in the drug product is justified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scaled batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three commercial scale batches per strength stored at 25°C/60% RH (1 batch per strength for 24 months, 2 batches per strength for 18 months), 30°C/75% RH (1 batch per strength for 24 months, 2 batches per strength for 18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 30 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for up to 4 hours in water, 5% dextrose in water, apple juice and apple puree.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for lactose have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Opixaf has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Opixaf is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Eliquis which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided,

which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apixaban is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Opixaf 5 mg film-coated tablets (Fidia Farmaceutici S.p.A., Italy) was compared with the pharmacokinetic profile of the reference product Eliquis 5 mg film-coated tablets (Bristol-Myers Squibb/Pfizer EEIG, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

For the 2.5 mg strength, a biowaiver was granted because the following requirements were met, in accordance with the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated at three different pHs (0.1, 4.5 and 6.8) according to the EMA Bioequivalence guideline. The f_2 statistics cannot be applied due to a high variability, so the 90% confidence interval of the f_2 similarity factor was calculated by bootstrapping. Similarity

between two dissolution profiles can be concluded when the lower limit of the 90% CI of f_2 is equal or greater than 50. The calculated f_2 similarity factor values were within criteria (>50%).

Bioequivalence study

Study 22-VIN-0263

Design

A single-dose, open label, balanced randomised, two-period, two-treatment, two-sequence, crossover oral bioequivalence study was carried out under fasting conditions in 28 healthy male subjects, aged 20-44 years. Each subject received a single dose (5 mg) of one of the two apixaban formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Apixaban may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of apixaban. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew consent after admission of the first period,and was replaced by an additional subject. A total of 28 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of apixaban, 5 mg under fasted conditions.

Treatment N=28	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1122 ± 213	1146 ± 208	112 ± 19	3.84 (2.00 – 4.50)
Reference	1213 ± 265	1245 ± 275	127 ± 21	3.01 (1.00 – 4.50)
***Ratio (90% CI)**	0.93 (0.88 – 0.97)	-	0.88 (0.82 – 0.94)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Opixaf 5 mg is considered bioequivalent with Eliquis 5 mg under fasted conditions.

The results of study 22-VIN-0263 with 5 mg formulation can be extrapolated to the other strength of 2.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Opixaf. At the time of approval, the most recent version of the RMP was version 0.2 dated 21 March 2025.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Bleeding
Important potential risks	• Liver injury • Potential risk of bleeding or thrombosis due to overdose or underdose

Missing information	• Use in patients with severe renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. For the safety concern of bleeding, a prescriber guide and a patient alert card is suggested as an additional risk minimisation measure. For the safety concern of potential risk of bleeding or thrombosis due to overdose or underdose, a prescriber guide is suggester as an additional risk minimisation measure.

Additional risk minimisation measures (including educational material)
The MAH will ensure that in each Member State where Opixaf is marketed, all healthcare professionals who are expected to prescribe Opixaf have access to/are provided with the following educational materials:

- Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

All patients and/or caregivers of paediatric patients who receive Opixaf will be provided with a Patient Alert Card (provided within each medicine pack).

Key Elements of the Prescriber guide:

- Details of populations potentially at higher risk of bleeding
- Recommended doses and guidance on the posology for different indications
- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Apixaban treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients and/or caregivers of paediatric patients should be provided with a Patient alert card and be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider
    - Importance of treatment compliance
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Apixaban if they need to have any surgery or invasive procedure

Key Elements of the Patient Alert Card:

- Signs or symptoms of bleeding and when to seek attention from a health care provider
- Importance of treatment compliance

- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Opixaf if they need to have any surgery or invasive procedure.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Eliquis. MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Eliquis 2.5 mg and 5 mg film-coated tablets, EU/1/11/691. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Opixaf 2.5 mg and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Eliquis 2.5 mg and 5 mg film-coated tablets. Eliquis is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Apixaban Pharamplot MFN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 October 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-